In-vivo beta-amyloid imaging in Alzheimer's disease

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The amyloid cascade hypothesis

- Altered Aβ production
  - ↑ Total Aβ (APP'Sw mutant, Trisomy 21)
  - ↑ Aβ42 (PS1, PS2, APP mutants)
  - More amyloidogenic Aβ (APP artic)

- Normal Aβ levels + APOE4

- Normal Aβ levels + aging

- Aβ aggregation and accumulation
  - Amyloid in plaques and vessels
  - Profibrils
  - Small oligomers
  - Intracellular aggregates

- Toxicity
  - Pro-inflammatory stimulus
  - ↑ Oxidative stress
  - Altered calcium homeostasis
  - Tau dysfunction and NFT formation
  - Other alteration in cellular homeostasis?

- Neuronal death and dysfunction

- Dementia

from: Golde 2003

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Progress of Amyloid Deposition in AD

*Thal et al., 2002*

**Stage A**

**Stage B**

**Stage C**

Aβ-amyloid protein

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PET tracers with high affinity ($K_i < 10 \text{ nM}$) to amyloid in human tissue

- 11C-labeled (half-life 20 min: cyclotron on-site)
  - *Pittsburgh Compound B (PiB)*
  - SB13, AZD2184
- 18F-labeled (half-life 90 min: can be used off-site)
  - Flutemetamol (GE-067, 3'-F-PIB)
  - Florbetaben (BAY-94-9172, AV-1)
  - Florbetapir (AV-45)
  - AZD-4694
Amyloid imaging with PET using a benzothiazole tracer (Pittsburgh compound B, C-11-PIB)

Normal subject: non-specific binding
Alzheimer’s disease: Cortical amyloid


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Technical aspects

- $^{11}$C-PIB injected dose typically 370 MBq
- Accumulation over up to 90 min
- DVR or SUVR (40-60 or 60-90 min p.i.) relative to cerebellar cortex

Price et al. JCBFM 2005

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Neuroscience Methods

NEWS

Alzheimer’s Biomarker Initiative Hits Its Stride

An effort to develop biomarkers for Alzheimer’s disease is churning out new data and making plans to expand.
Collaborating partners on neurodegenerative disease

A. Nordberg & coll, Karolinska Institutet, Stockholm, Sweden;
J. Rinne & coll, Turku University, Turku, Finland;
A. Drzezga & coll, Technische Universität, Munich, Germany;
D. Brooks & coll, Imperial College, London, United Kingdom;
K. vanLaere & coll, Katholieke Universiteit Leuven, Leuven, Belgium;
Vita Salute San Raffaele University, Milan, Italy;
University of Cologne, Cologne, Germany
University of Manchester, Manchester, United Kingdom
Central image data processing

- Reconstructed images (Siemens HR+, GE Advance)
  - 40-60 min after injection of 200-400 MBq C-11-PIB (n=238)
- Spatially normalised sample-based PIB image template
  - Based on nonlinear coregistration (SPM5-DARTEL) of 151 MRIs
- Coregistration of all PET images to template (SPM5)
- Automated placement of volumes of interest (VOIs)
  - Cerebellar cortex
    - median provides denominator for uptake ratios
  - Cerebral cortex (grey matter) and putamen (Hammers et al., 2003)
- Calculation of regional PIB uptake (SUVR)
- Quality control (inclusion criteria, data completeness, spatial normalisation)
  - Exclusion of 18 data sets: n=220

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# Demographic & clinical data

<table>
<thead>
<tr>
<th></th>
<th>CG</th>
<th>n</th>
<th>MCI</th>
<th>n</th>
<th>AD</th>
<th>n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 51)</td>
<td></td>
<td>(n = 72)</td>
<td></td>
<td>(n = 97)</td>
<td></td>
<td>MCI-CG/AD-CG/MCI-AD</td>
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<tr>
<td><strong>Demographics</strong></td>
<td></td>
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</tr>
<tr>
<td>Age (years)</td>
<td>67.4 (6.3)</td>
<td>51</td>
<td>67.5 (8.1)</td>
<td>72</td>
<td>69.2 (8.4)</td>
<td>97</td>
<td>n.s.</td>
</tr>
<tr>
<td>Men</td>
<td>22 (43%)</td>
<td>51</td>
<td>37 (51%)</td>
<td>72</td>
<td>47 (49%)</td>
<td>97</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>ApoE genotyping</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>homozgyous non-E4/ non-E4</td>
<td>21 (68%)</td>
<td>31</td>
<td>25 (42%)</td>
<td>59</td>
<td>23 (27%)</td>
<td>86</td>
<td><strong>/</strong>*/n.s.</td>
</tr>
<tr>
<td>heterozygous non-E4/ E4</td>
<td>10 (32%)</td>
<td>-</td>
<td>18 (31%)</td>
<td>16 (27%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>homozgyous E4/ E4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>Neuropsychological data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>29.2 (1.1)</td>
<td>43</td>
<td>27.1 (2.0)</td>
<td>72</td>
<td>24.0 (3.2)</td>
<td>97</td>
<td><strong>/</strong><em>/</em>**</td>
</tr>
<tr>
<td>Verbal memory immediate (Z)</td>
<td>0.6 (1.0)</td>
<td>36</td>
<td>-1.0 (1.7)</td>
<td>64</td>
<td>-1.9 (1.4)</td>
<td>90</td>
<td><strong>/</strong><em>/</em>**</td>
</tr>
<tr>
<td>Verbal memory delayed (Z)</td>
<td>0.9 (0.9)</td>
<td>38</td>
<td>-1.2 (1.5)</td>
<td>64</td>
<td>-2.2 (1.2)</td>
<td>90</td>
<td><strong>/</strong><em>/</em>**</td>
</tr>
<tr>
<td>Non-verbal memory, delayed (Z)</td>
<td>0.7 (1.2)</td>
<td>28</td>
<td>-0.3 (1.7)</td>
<td>60</td>
<td>-1.7 (1.0)</td>
<td>71</td>
<td><strong>/</strong><em>/</em>**</td>
</tr>
<tr>
<td>Visuoconstruction(Z)</td>
<td>0.9 (0.6)</td>
<td>28</td>
<td>-0.8 (1.3)</td>
<td>60</td>
<td>-1.0 (1.8)</td>
<td>70</td>
<td><strong>/</strong>*/n.s.</td>
</tr>
<tr>
<td>Verbal fluency (Z)</td>
<td>0.3 (1.0)</td>
<td>30</td>
<td>-0.7 (1.2)</td>
<td>44</td>
<td>-1.1 (1.0)</td>
<td>50</td>
<td><strong>/</strong>*/n.s.</td>
</tr>
<tr>
<td>TMT A (Percentiles)</td>
<td>35.8 (32.7)</td>
<td>37</td>
<td>19.5 (26.7)</td>
<td>49</td>
<td>13.4 (17.9)</td>
<td>74</td>
<td>*/**/n.s.</td>
</tr>
<tr>
<td>TMT B (Percentiles)</td>
<td>44.9 (28.4)</td>
<td>36</td>
<td>19.1 (27.5)</td>
<td>49</td>
<td>10.8 (21.2)</td>
<td>74</td>
<td><strong>/</strong>*/n.s.</td>
</tr>
</tbody>
</table>

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Bimodal PIB uptake in normal controls

Low-uptake cluster:
Mean 1.258, SD 0.073
Upper 95% normal confidence limit 1.41
## Frequency of abnormal PIB uptake in diagnostic groups

<table>
<thead>
<tr>
<th>Dg</th>
<th>CON</th>
<th>PIB normal</th>
<th>increased &quot;PIB+&quot;</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Count</td>
<td></td>
<td>Count</td>
</tr>
<tr>
<td>Dg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CON</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI</td>
<td></td>
<td>25</td>
<td>47</td>
<td>72</td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td>10</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>81</td>
<td>139</td>
<td>220</td>
</tr>
<tr>
<td>% within Dg</td>
<td>36.8%</td>
<td>63.2%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

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Normal controls

- Most normal controls have cortical uptake (relative to cerebellar cortex) within a narrow range of 1.0 to 1.5
- Depending on age, some individuals with normal cognition may have abnormally high uptake
  - Approx. 10% at age < 75 (DiMI)
  - Up to 40% at higher age (ADNI)
  - Indication of increased risk for AD, but clinical significance not yet known
Correspondence between abnormal in-vivo and postmortem amyloid in normals controls

Villemaigne et al. 2008; Davies et al. 1988
11C-PIB in normal controls
(Morris et al., Arch Neurol, 2009)

9 subjects developed dementia within 1 to 5.5 years
14 additional subjects progressed CDR 0.5 without dementia: MCBP n.s.

Conclusion: Positive amyloid scan is indicating an increased risk for clinical AD in normal controls

Table 1. Characteristics of 159 Cognitively Normal Individuals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.5 (8.6)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>69.8</td>
</tr>
<tr>
<td>African American race, %</td>
<td>10.7</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.6 (2.5)</td>
</tr>
<tr>
<td>APOE ε4 carrier, %</td>
<td>31.5</td>
</tr>
<tr>
<td>MMSE score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29.0 (1.2)</td>
</tr>
<tr>
<td>Follow-up time, y</td>
<td>2.4 (1.3)</td>
</tr>
</tbody>
</table>

Abbreviation: MMSE, Mini-Mental State Examination.
<sup>a</sup>Range of possible scores, 30 (best) to 0 (worst).

Table 2. Cox Proportional Hazards Model Testing MCBP for PiB as a Predictor of Time to DAT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCBP</td>
<td>4.82 (1.22-19.01)</td>
<td>.02</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.14 (1.02-1.28)</td>
<td>.03</td>
</tr>
<tr>
<td>Education, y</td>
<td>0.91 (0.69-1.19)</td>
<td>.49</td>
</tr>
<tr>
<td>APOE ε4 carrier</td>
<td>0.98 (0.20-4.90)</td>
<td>.98</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.54 (0.10-2.90)</td>
<td>.48</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DAT, dementia of the Alzheimer type; HR, hazard ratio; MCBP, mean cortical binding potential; PiB, Pittsburgh Compound B.

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Amyloid PET in MCI
Forsberg et al., Neurobiol Aging, 2007
Dementia-free survival in MCI: dementia develops in PIB+ subjects only

PIB uptake level
- PIB negative
- PIB+ < median
- PIB+ > median

Follow-up [m]

Cum Survival

0.00 10.00 20.00 30.00 40.00 50.00 60.00

P<0.001

Moderate vs. high PIB uptake: not significant

Negative predictive value: 100%
Positive predictive value (dementia within 2 yrs): 50%

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PIB uptake & memory in MCI

All MCI:
\[ R = -0.49, \quad p < 0.001 \]

PIB+ only:
\[ R = -0.28, \quad \text{n.s.} \]
Neocortical PIB uptake by center & diagnosis

![Box plot showing PIB uptake by center and diagnosis. The x-axis represents different diagnoses (A_CON, B_MCI, C_AD), and the y-axis represents composite cortex uptake. The box plot indicates the distribution of PIB uptake across different centers and diagnoses.]
Amyloid PET and genetics

• More cortical amyloid in apolipoprotein E4 allele carriers

• Level of in-vivo cortical amyloid binding is a genetic trait (Hinrichs et al., 2009) – beyond dependency on ApoE4

• More amyloid in striatum in carriers of APP locus duplication (Remes et al., 2008) than in sporadic AD
Correlation with CSF A-beta

Tolboom et al., JNM, 2009
See also: Jagust et al., 2009; Fagan et al., 2006
Amyloid versus FDG PET

- **Specificity**
  - Amyloid: molecular specificity (plaques & vascular amyloid)
  - FDG: Indirect, by regional distribution

- **Sensitivity:** time of first positive scan before onset of dementia
  - Amyloid: detection already in preclinical AD (up to 10 years?)
  - FDG: 1-2 years

- **Influence of age**
  - Amyloid: Increasing frequency of positive scans in normal controls
  - FDG: Loss of sensitivity (less contrast, global decrease of CMRglc)

- **Influence of cerebral microvascular disease**
  - Amyloid: unknown
  - FDG: Loss of sensitivity (global decrease of CMRglc)

- **Relation with cognitive function**
  - Amyloid: weak at early stages, absent in manifest AD (thus complementing clinical findings)
  - FDG: close (potential surrogate outcome marker)
Current status of amyloid PET in AD

• **Very high sensitivity** (> 90%) for detection of amyloid deposition
  – Detection at very early stage, even before onset of clinical symptoms
  – Few suspected AD cases so far reported with normal PIB uptake (Cairns et al. 2009)
• **Very good specificity**
  – No uptake in FTD (Rabinovici et al. 2007, Rowe et al., 2008)
  – No uptake in most cases with Parkinson's disease and dementia (Maetzler et al. 2008)
  – Most patients with Lewy-body dementia show increased uptake (Edison et al., 2008), consistent with pathological findings
  – Negative in prion disease (Boxer et al. 2007, Villemagne et al. 2009)
• **Excellent negative predictive value** (close to 100%) in MCI
• PIB provides robust signal in multicenter studies

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Fluorinated PIB analogues:
Flutemetamol

180 MBq  Nelissen et al., JNM, 2009
Florbetaben (BAY-94-9172, AV-1)

Normal controls

AD

FTD

300 MBq, 90-120 min, Rowe et al., Lancet Neurol., 2008

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18F-AV-45 on HRRT-PET

Normal control

250 MBq
10-60 min

Fronto-temporal dementia

Alzheimer's Disease
18F-FDDNP

- Different binding site than PIB
  - Competing with binding of nonsteroidal antiphlogistics
- Significant affinity also to tau deposits
  - Imaging of neurofibrillary tangles?
- Gradually increased hippocampal uptake in MCI and AD

Small et al., NEJM, 2006

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18F-FDDNP also binds to neurofibrillary tangles, with preferential location in mesial temporal cortex

Neocortical PIB (amyloid) versus hippocampal FDDNP (tau) in Alzheimer's disease

Tolboom et al., JNM, 2009

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Further studies

• Practical automated & standardised quantitative analysis for multicenter use as biomarker

• Scientific studies exploring the role of amyloid and other factors (e.g. vascular, tau, inflammation) for progression to dementia in amyloid-positive non-demented subjects
  – Amyloid in striatum apparently not causing neurodegeneration
  – Little amyloid in hippocampus, but very early neurodegeneration (intracellular tau deposits)
  – Early plateau of amyloid binding already at MCI stage
  – Removal of amyloid does not necessarily stop neurodegeneration (AN1792 trial; Holmes et al., Lancet, 2008)

• New tracers for oligomeric amyloid (not seen on amyloid scans, but probably the most neurotoxic amyloid species)
Diagnostic categories for AD prior to onset of dementia

• Preclinical AD
  – The long asymptomatic period between the first brain lesions and the first appearance of symptoms which concerns normal individuals that later fulfil AD diagnostic criteria

• Prodromal AD
  – The symptomatic predementia phase of AD, generally included in the mild cognitive impairment category; this phase is characterised by symptoms not severe enough to meet currently accepted diagnostic criteria for AD

Dubois et al., Lancet Neurology, 2007
Amyloid scanning as biomarker in phase I/II therapeutic drug trials

• Preventive treatment
  – Identify subjects with preclinical AD
  – Potential for monitoring amyloid accumulation

• Disease-modifying treatment
  – Identify prodromal AD in MCI patients
  – Potential for monitoring the reduction of amyloid load (and whether that correlates with other biomarkers and clinical parameters)
Collaborators & funding

- **University of Manchester:**
  Rainer Hinz, Stephen F. Carter, Emma Vardy, Tobias Langheinrich, Gavin Brown, Jose Anton, David Neary, Julie Snowden, Alex Gerhard

- **DiMI (EC FP7):**

- **AVID (contracted research):**
  Dan Skovronski, Mike Pontecorvo

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